IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SANTARUS, INC., a Delaware corporation, and THE CURATORS OF THE UNIVERSITY OF MISSOURI, a public corporation and body politic of the State of Missouri,	)	
Plaintiffs,	)	C.A. No. 07-551-GMS
v.	)	(CONSOLIDATED)
PAR PHARMACEUTICAL, INC., a Delaware corporation,	)	
Defendants	)	

DECLARATION OF STEVEN J. FINEMAN

I, Steven J. Fineman, declare as follows:

1. I am an attorney at Richards, Layton & Finger, P.A., and submit this declaration in support of Defendant Par Pharmaceuticals Inc.'s Opening Claim Construction Brief Regarding U.S. Patent Nos. 6,489,346; 6,699,885; and 6,645,988.

2. Attached hereto as Exhibit A is a true and correct copy of the record for the omeprazole product Prilosec found in the United States' Food and Drug Administration's *Approved Drug Products with Therapeutic Equivalence Evaluations* (28th ed. 2008) ("*Orange Book*").

3. Attached hereto as Exhibit B is a true and correct copy of United States Patent No. 3,621,094.

4. Attached hereto as Exhibit C is a true and correct copy of United States Patent No. 4,316,888.

5. Attached hereto as Exhibit D is a true and correct copy of the *Orange Book's* "Patent and Exclusivity List" records for Zegerid® and the *Orange Book's* corresponding "Patent and Exclusivity Terms" for Zegerid®.

6. Attached hereto as Exhibit E is a true and correct copy of the definition of the term "solid," as found in *Stedman's Online Medical Dictionary's*, *available at* http://www.stedmans.com/section.cfm/45 (last accessed Aug. 21, 2008) (referring to *Stedman's Medical Dictionary,* 27th ed.).

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 22nd day of August, 2008.

Steven J. Fineman

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on August 22, 2008, I electronically filed the foregoing document with the Clerk of Court using CM/ECF which will send notification of such filing(s) and Hand Delivered to the following:

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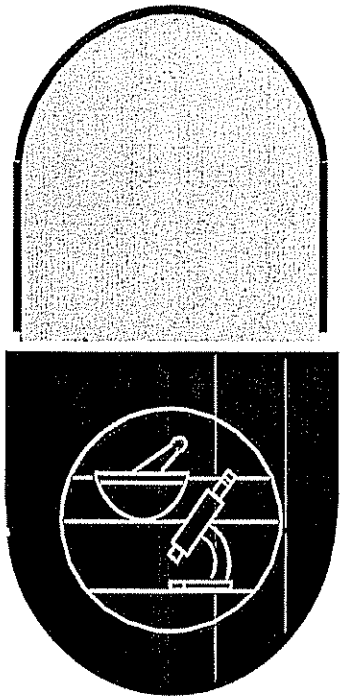
EXHIBIT A



APPROVED DRUG PRODUCTS

WITH

THERAPEUTIC EQUIVALENCE EVALUATIONS

28th EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL SCIENCE
OFFICE OF GENERIC DRUGS

2008

OLMESARTAN MEDOXOMIL

TABLET; ORAL

BENICAR

+	DAIICHI SANKYO	40MG	N21286	004	Apr 25, 2002

OLOPATADINE HYDROCHLORIDE

SOLUTION/DROPS; OPHTHALMIC

PATADAY

+	ALCON	0.2%	N21545	001	Dec 22, 2004

PATANOL

+	ALCON	EQ 0.1% BASE	N20688	001	Dec 18, 1996

OLSALAZINE SODIUM

CAPSULE; ORAL

DIPENTUM

+	UCB INC	250MG	N19715	001	Jul 31, 1990

OMEGA-3-ACID ETHYL ESTERS

CAPSULE; ORAL

LOVAZA

+	RELIANT PHARMS INC	1GM	N21654	001	Nov 10, 2004

OMEPRAZOLE

CAPSULE, DELAYED REL PELLETS; ORAL

OMEPRAZOLE

AB		APOTEX	10MG	N76048	001	Oct 22, 2007
AB			20MG	N76048	002	Oct 22, 2007
AB		DR REDDYS LABS LTD	10MG	N75576	003	Oct 22, 2007
AB			20MG	N75576	002	Oct 22, 2007
AB		IMPAX LABS	10MG	N75785	001	Oct 22, 2007
AB			20MG	N75785	002	Oct 22, 2007
AB		KREMERS URBAN DEV	10MG	N75410	001	Nov 01, 2002
AB			20MG	N75410	002	Nov 01, 2002
AB		LEK PHARMS	10MG	N75757	001	Jan 28, 2003
AB			20MG	N75757	002	Jan 28, 2003
AB		MYLAN	10MG	N75876	001	May 29, 2003
AB			20MG	N75876	002	May 29, 2003

PRILOSEC

AB		ASTRAZENECA	10MG	N19810	003	Oct 05, 1995
AB	+		20MG	N19810	001	Sep 14, 1989

PRILOSEC

+	ASTRAZENECA	40MG	N19810	002	Jan 15, 1998

OMEPRAZOLE; SODIUM BICARBONATE

CAPSULE; ORAL

ZEGERID

	SANTARUS	20MG;1.1GM	N21849	001	Feb 27, 2006
+		40MG;1.1GM	N21849	002	Feb 27, 2006

FOR SUSPENSION; ORAL

ZEGERID

	SANTARUS	20MG/PACKET;1.68GM/PACKET	N21636	001	Jun 15, 2004
+		40MG/PACKET;1.68GM/PACKET	N21636	002	Dec 21, 2004

ONDANSETRON

TABLET, ORALLY DISINTEGRATING; ORAL

ONDANSETRON

AB		BARR	4MG	N76693	001	Jun 25, 2007
AB			8MG	N76693	002	Jun 25, 2007
AB		GLENMARK PHARMS INC	4MG	N78152	001	Jun 27, 2007
AB			8MG	N78152	002	Jun 27, 2007
AB		KALI LABS	4MG	N76506	001	Dec 26, 2006

EXHIBIT B

United States Patent

[11] 3,621,094

[72] Inventors David Mayron
Whitpain Township;
Frank J. Tiano, Philadelphia, both of Pa.

[21] Appl. No. 719,234
[22] Filed Apr. 5, 1968
[45] Patented Nov. 16, 1971

[73] Assignee Smith Kline & French Laboratories
Philadelphia, Pa.

[54] CONCENTRATED AQUEOUS LIQUID ANTACID COMPOSITIONS CONTAINING CERTAIN PHOSPHATE AND GLUCONATE SALTS

6 Claims, No Drawings

[52] U.S. Cl. 424/128, 424/127, 424/131, 424/154, 424/155, 424/156, 424/157, 424/158, 424/180, 424/319

[51] Int. Cl. A61k 27/00

[50] Field of Search 424/128, 131, 154, 155, 156, 157, 158, 180, 127, 319

[56] References Cited

UNITED STATES PATENTS

3,062,714	11/1962	Pitkin et al.	424/128
3,215,601	11/1965	Stolar	424/128
3,361,769	1/1968	Halpern et al.	424/180

OTHER REFERENCES

Merck Index, 5th Edition, 1940, page 109
Merck Index, 5th Edition, 1940, page 109

Primary Examiner—Albert T. Meyers
Assistant Examiner—Daren M. Stephens
Attorneys—William H. Edgerton, Richard D. Foggio, Joan S. Keps, Arthur R. Eglington, Alan D Lourie and Joseph A. Marlino

ABSTRACT: Pharmaceutically elegant aqueous pharmaceutical suspensions having antacid and antiulcer activity comprising a high concentration of antacid and a combination of calcium phosphate monobasic and a nontoxic alkali metal or alkaline earth gluconate salt such as sodium, potassium, calcium or magnesium gluconate.

CONCENTRATED AQUEOUS LIQUID ANTACID COMPOSITIONS CONTAINING CERTAIN PHOSPHATE AND GLUCONATE SALTS

This invention relates to new pharmaceutically elegant antacid compositions. More specifically, this invention relates to aqueous pharmaceutical suspensions for oral use having antacid and antiulcer properties which contain a high concentration of antacid but which are also pharmaceutically stable and very palatable.

Therapeutically, antacids are used for the treatment of gastric hyperacidity, dyspepsia and peptic ulcers. Antacids have played a major role in the clinical management of peptic ulcers and in appropriate doses to relieve the plain of this condition.

One of the major disadvantages of using the currently available liquid antacid preparations for ulcer therapy is that they necessarily contain a low concentration, approximately 8 percent, of active antacid ingredient. These commercially available antacid preparations are rapidly and readily eliminated from the stomach as it empties. After a 30-minute period not enough antacid remains to provide effective antacid or antiulcer activity. In an attempt to overcome this short duration of action and to obtain a sustained protective effect recent therapy comprises administering the prior art liquid antacid preparations at hourly intervals. Even when these are administered within these frequent hourly intervals the desired therapeutic effect, maintenance of gastric pH above 3.5, is frequently lost between doses. This procedure also makes it difficult, if not impossible, to control the gastric acidity during the sleeping hours.

It is also apparent that because of the low concentration of current liquid antacid preparations this method of therapy, particularly for peptic ulcers, involves the oral administration of continuous and large daily volumes of antacid to keep the gastric contents neutralized. The administration of larger volumes of the commercial liquid antacid suspensions per does has proven very impractical. Most important, it has been demonstrated that increasing the volume of the suspension does not increase the duration of action and produces substantially the same therapeutic effect. Secondly, increasing the volume of antacid per dose would result in a serious personal discomfort and expense.

A further disadvantage is that even commercially available antacid products have well recognized stability problems. One of these is their tendency to coagulate and clump upon standing. Further, the palatability of the prior art liquid antacids is very objectionable, i.e. they have a chalky and astringent taste. These problems are multiplied as the concentration of antacid increase.

It is therefore the object of this invention to provide more concentrated forms of liquid antacid suspensions which are stable and palatable but still provide for prompt and long-acting antacid and antiulcer activity, i.e., antacid and ulcer protection well beyond the normal gastric emptying time and of sufficient duration of effective activity to maintain the gastric contents at a desirable pH between doses.

Unexpectedly the preparations of this invention offer a much more concentrated form of antacid preparation than has been previously available. If such a concentration could be prepared in the vehicle of the prior art antacid preparation it would resemble a slightly damp chalk powder. This invention therefore provides a more convenient, stable and palatable liquid for antacid therapy. The preparation in accordance with this invention can contain as high as 50 percent antacid which represents more than a fivefold increase in concentration over the commercially available liquid antacid preparations.

The novel pharmaceutical preparations of this invention are unique in that they are not only much more concentrated than the commercially available antacid preparations but are also more pharmaceutically elegant. These antacid suspensions are more stable and have improved palatability being free of the gritty, astringent, chalky taste which is so prevalent even with the previously known antacid compositions.

The novel pharmaceutical compositions of this invention are also unique in that they provide for improved concentrated liquid antacid formulations of the type which promptly neutralize gastric acidity and maintain this neutralization over an extended period of time. In accordance with this invention, an improved antacid preparation is provided which increases both the degree and duration of action of the antacid and assures adequate antacid and antiulcer protection between doses. When equal volumes of a representative liquid antacid preparation of this invention and the leading commercial antacid preparation are administered orally in standard tests the preparation of this invention exerts antiulcer activity over twice as long as does the prior art antacid preparation.

A still further advantage of the concentrated antacid composition of this invention is due to its high concentration. It eliminates the necessity of administering large daily volumes of antacid to obtain a therapeutic effect. The frequency of administration is greatly diminished when using the concentrated pharmaceutical composition of this invention.

The novel pharmaceutical composition of this invention comprises an aqueous suspension comprising a high concentration of antacid and a combination of calcium phosphate monobasic and a pharmaceutically acceptable, nontoxic alkali earth or alkali metal gluconate especially sodium, potassium, magnesium or calcium gluconate. Most advantageously, the aqueous suspension will comprise the antacid in combination with calcium phosphate monobasic and calcium gluconate. It has been unexpectedly discovered that the addition of calcium phosphate monobasic and at least one of the above-noted gluconate salts permit a much higher concentration of antacid in an aqueous suspension than has previously been possible. The employment of the combination of these additives has the further added advantage in that it not only produces an aqueous suspension of an antacid having a high concentration but it also provides for a palatable and stable preparation. The presence of calcium phosphate monobasic and a gluconate salt in the aqueous vehicle effectively prevents the suspended antacid from clumping or caking at the bottom of the container thus insuring proper dosage by simple shaking before use.

It has been discovered that these additives must be present in combination in order to achieve the advantages of stability and palatability noted above. If either the monobasic calcium phosphate or one of the disclosed gluconate salts is employed alone to prepare a concentrated aqueous antacid suspension the resulting composition will slowly thicken, then solidify into a nonpourable mass. When these additives are used in combination the resulting concentrated antacid suspension results in the described pharmaceutically elegant preparation.

Advantageously, the monobasic calcium phosphate and the alkali gluconate salt, preferably calcium gluconate, will each be present in an amount of from about 0.5 percent to about 7.0 percent by weight/volume of the liquid suspension. Most advantageously, the calcium phosphate monobasic and calcium gluconate will each be present in an amount of from about 2.0 percent to about 5.0 percent by weight/volume of the liquid suspension. The total concentration of the additives will be present in an amount of about 3 percent to about 10 percent.

By the term high concentration of antacid is meant that the antacid ingredient is present up to about 50 percent weight/volume. Preferably, the antacid 50 present from about 25 percent to about 50 percent weight/volume, most advantageously from about 30 percent to about 45 percent weight/volume. Of course, lower concentrations of antacid can be used in the described vehicle of this invention if one desires a conventional antacid preparation of increased elegance.

The antacid employed may be any of the conventional antacids well known to the art. For example, the antacid may be calcium carbonate, magnesium oxide, magnesium trisilicate, magnesium carbonate, aluminum hydroxide, bismuth subcarbonate, dihydroxy aluminum aminoacetate, bismuth alu-

minate, aluminum oxyhydroxide, sodium bicarbonate, magnesium hydroxide, sodium carbonate and aluminum phosphate or combinations thereof such as, for example, aluminum hydroxide-magnesium hydroxide glycine dried gel and aluminum hydroxide-magnesium carbonate codried gel.

The above aqueous concentrated antacid suspensions are made following the techniques described hereafter. When are made following the techniques described hereafter. When necessary, any desired pharmaceutically compatible adjuvant used in liquid preparations by those skilled in the art may be employed. For example, preservatives such as methylparaben, or propylparaben, flavoring agents such as oil of orange, lemon-lime flavors, raspberry flavor, cola flavors, mint flavors or the combination of these flavors or any solubilizing agent such as glycerin or propylene glycol may be employed. Further, antispasmodic agents, tranquilizers or other medicaments can be optionally included in the preparation.

The invention will be further clarified by the following specific examples. These examples are not limiting but are used to make obvious to one skilled in the art the full practice of the method of this invention.

EXAMPLE 1

Ingredients	Amount
Aluminum hydroxide, NF	18.90 gm
Magnesium hydroxide, NF	11.07 gm
Precipitated calcium carbonate, USP	7.50 gm
Cetyl dimethyl benzyl ammonium chloride	0.01 gm
Glycine	9.00 gm
Calcium cyclamate	0.30 gm
Calcium phosphate monobasic	3.75 gm
Calcium gluconate	2.00 gm
Hydroxypropyl	0.12 gm
Antifoam emulsion	0.01 gm
Peppermint flavor	0.10 ml
Water, USP qs	ad 100.00 ml

The cetyl dimethyl benzyl ammonium chloride is dissolved in 65 ml. of water. The aluminum hydroxide, magnesium hydroxide and glycine are evenly suspended in the solution. The calcium gluconate and calcium phosphate monobasic are then added. The calcium carbonate, hydroxypropyl methylcellulose and antifoam are also added to the suspension with gently agitation. The flavor is added and the suspension is brought to the desired volume by the addition of sufficient water.

EXAMPLE 2

Ingredients	Amount
Aluminum hydroxide, NF	22.70 gm
Magnesium hydroxide, NF	13.28 gm
Precipitated calcium carbonate, USP	9.00 gm
Cetyl dimethyl benzyl ammonium chloride	0.01 gm
Calcium cyclamate	0.03 gm
Calcium phosphate monobasic	3.00 gm
Calcium gluconate	3.00 gm
glycerin	10.50 ml
Lemon-lime flavor	0.01 ml
Water, USP qs	ad 100.00 ml

The cetyl dimethyl benzyl ammonium chloride is dissolved in 65 ml. of water. The aluminum hydroxide and magnesium hydroxide are evenly suspended in the solution. The calcium gluconate and calcium phosphate monobasic are added with agitation, then the calcium carbonate, calcium cyclamate and glycerin are added to the suspension with gentle agitation. The flavor is then added and the suspension is brought to the desired volume by the addition of sufficient water.

EXAMPLE 3

Ingredients	Amount
Aluminum hydroxide, NF	27.5 gm
Methylparaben	0.045 gm
Propylparaben	0.020 gm
Propylene glycol	5.00 ml
Calcium phosphate monobasic	3.00 gm
Sodium gluconate	2.50 gm
Imitation wintergreen	0.25 ml
Purified water qs	ad 100.00 ml

Aluminum hydroxide is evenly suspended in 65 ml. of water and the calcium phosphate monobasic and sodium gluconate are added. The parabens are dissolved in the propylene glycol with the aid of heat and added to the suspension. The flavor is then added and the suspension is brought to the desired volume by the addition of sufficient water.

EXAMPLE 4

Ingredients	Amount
Aluminum hydroxide, NF	28.00 gm
Magnesium carbonate, NF	5.10 gm
Cetyl dimethyl benzyl ammonium chloride	0.01 gm
Calcium cyclamate	0.30 gm
Calcium phosphate monobasic	3.75 gm
Magnesium gluconate	2.00 gm
Hydroxypropyl methylcellulose	0.12 gm
Peppermint flavor	0.05 ml
Water, USP	ad 100.00 ml

The cetyl dimethyl benzyl ammonium chloride is dissolved in 65 ml. of water. The aluminum hydroxide and magnesium carbonate are evenly suspended in the solution. The magnesium gluconate and calcium phosphate monobasic are added with agitation, then the hydroxypropyl methylcellulose and calcium cyclamate are added to the suspension with gentle agitation. The flavor is then added and the suspension is brought to the desired volume by the addition of sufficient water.

What is claimed is:

1. A pharmaceutically elegant liquid pharmaceutical composition for oral use comprising from about 25 percent to about 50 percent of a solid antacid material comprising aluminum hydroxide, magnesium hydroxide, calcium carbonate, magnesium oxide, magnesium trisilicate, magnesium carbonate, bismuth subcarbonate, dihydroxy aluminum aminoacetate, bismuth aluminate, aluminum oxyhydroxide, sodium bicarbonate, sodium carbonate, aluminum phosphate, glycine or combinations thereof suspended in an aqueous vehicle containing from about 0.5 percent to about 7.0 percent weight/volume of monobasic calcium phosphate and at least one of sodium, potassium, calcium or magnesium gluconates the total concentrations of phosphate and gluconate being from about 3 percent to about 10 percent.

2. The pharmaceutical composition of claim 1 wherein the gluconate salt is calcium gluconate.

3. The pharmaceutical composition of claim 1 wherein the antacid is present from about 30 percent to about 45 percent weight/volume and the monobasic calcium phosphate and calcium gluconate are each present in an amount of from about 2.0 percent to about 5.0 percent.

4. The pharmaceutical composition of claim 2 wherein the antacid is magnesium hydroxide, aluminum hydroxide, magnesium carbonate, calcium carbonate or combinations thereof.

5. The pharmaceutical composition of claim 1 in which the antacid is at least one of aluminum hydroxide, magnesium carbonate or calcium carbonate.

6. The pharmaceutical composition of claim 1 in which the essential ingredients in the aqueous vehicle comprise about 19 percent aluminum hydroxide, about 11 percent magnesium hydroxide, about 7.5 percent calcium carbonate, about 3.7percent calcium phosphate monobasic, and about 2 percent calcium gluconate.

* * * * *

EXHIBIT C

United States Patent [19]

Nelson

[11] 4,316,888

[45] Feb. 23, 1982

[54] METHOD AND COMPOSITION OF REDUCING PAIN

[75] Inventor: Eric L. Nelson, Santa Ana, Calif.

[73] Assignee: Nelson Research & Development Co., Irvine, Calif.

[21] Appl. No.: 140,493

[22] Filed: Apr. 15, 1980

[51] Int. Cl.³ A61K 33/00; A61K 33/10; A61K 33/08; A61K 31/485

[52] U.S. Cl. 424/127; 424/156; 424/157; 424/184; 424/260

[58] Field of Search 424/157, 260, 127, 184, 424/156, 155, 244

[56] References Cited

U.S. PATENT DOCUMENTS

2,934,472	4/1960	May	424/184
3,108,041	10/1963	Weiner	424/260
3,140,978	7/1964	Zentner	424/260
3,427,379	2/1969	Barry et al.	424/260
3,767,794	10/1973	McVean et al	424/184
3,919,237	11/1973	Halder	424/260

OTHER PUBLICATIONS

Chemical Abstracts, vol. 82, 1975, 93155k.

The Merck Index, Ninth Ed. (1976), Merck & Co. Rahway, N.J., article 7908.

The Merck Index, Ninth Ed., Merck & Co. Inc., Rahway, N.J. 1976, pp. 990, 1112, 48 and App-1.

Handbook of Nonprescription Drugs, pub. by American Pharm. Assoc., Wash., D.C. 1977, pp. 84, 89, 91, 94, 97–100, 109, 102–104, 106, 108.

Life Sciences, vol. 15, pp. 1665–1672, No. 9

Primary Examiner—Frederick E. Waddell

Attorney, Agent, or Firm—Martin A. Voet

[57] ABSTRACT

A method for temporarily reducing pain in animals including humans, and especially pain associated with gastrointestinal dysfunction, by administering to an animal having pain an effective, pain reducing amount of dextromethorphan, preferably as the hydrobromide.

10 Claims, No Drawings

METHOD AND COMPOSITION OF REDUCING PAIN

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to a method of treatment for pain. More particularly the invention relates to a method for temporarily reducing pain in humans associated with gastrointestinal dysfunctions such as peptic ulcer.

2. Background of the Prior Art

A peptic ulcer is a circumscribed discontinuity in the surface of the gastrointestinal mucosa which occurs in areas bathed by acid-pepin. Peptic ulcers are classified according to location, that is, gastric, duodenal, esophageal or marginal.

The major symptom of chronic duodenal ulcer disease is pain in the epigastrium. The "testbook" periodic pain syndrome of nonradiating epigastric pain, characterized by onset one to three hours after eating, relief by food, antacids, or vomiting, absence before breakfast, but frequently awakening the patient at night and occurring in clusters of daily pain for a few weeks followed by longer pain free intervals, is actually present in at least 50 percent of duodenal ulcer patients. Many patients have varied descriptions of the character of the pain, for example, discomfort, heartburn, cramping, burning and gnawing.

Cause of ulcer pain is unknown. There are numerous, poorly controlled studies that report pain relief with mechanical or chemical removal of acid and some controlled studies that cast doubt on the pain-relieving qualities of antacids.

Endoscopic observation fails to correlate subjective "degree of pain" with size or depth of ulcer.

SUMMARY OF THE INVENTION

Dextromethorphan is an old compound used heretofore as an antitussive. It is marketed in a wide variety of "over-the-counter" (OTC) and prescription (Rx) products for relief of cough, typically as the hydrobromide. It is described in the art consistently as having no known analgesic activity.

Notwithstanding the long established belief that dextromethorphan has no analgesic activity, it has now been discovered that dextromethorphan is useful in the temporary reduction of pain and especially pain associated with gastrointestinal dysfunction.

More particularly, the invention relates to a method of temporarily reducing pain in animals comprising administering to an animal having pain an effective, pain reducing amount of dextromethorphan.

The invention also relates to a method for temporarily reducing pain associated with gastrointestinal dysfunction in humans comprising administering to a human having pain associated with gastrointestinal dysfunction, an effective, pain reducing amount of dextromethorphan hydrobromide.

The invention further relates to pharmaceutical compositions comprising an effective, pain reducing amount of dextromethorphan and preferably dextromethorphan hydrobromide in combination with one or more of the following:

(1) An effective, gastric acid secretion inhibiting amount of a histamine H_2 receptor antagonist, such as cimetidine; or

(2) An effective acid neutralizing amount of an antacid; or

(3) An effective acid neutralizing amount of an anticholinergic drug, such as atropine, belladonna, homatropine, methscopolamine bromide and scopolamine hydrobromide, or

(4) An effective gas reducing amount of an antiflatulent, such as simethicone.

DETAILED DESCRIPTION OF THE INVENTION

Dextromethorphan (d-3-methoxy-N-methylmorphinan) is the d-isomer of the codeine analog of levophornal; however, unlike the l isomer, it has consistently been reported by the prior art as having no analgesic properties. The compound is well known in the art as a cough suppressant (antitussive) and is commercially available; e.g., U.S. Pat. No. 2,676,177 and Höfliger et al, Helv. Chim. Acta 39, 2053 (1956). The hydrobromide salt of dextromethorphan is widely commercially used as an "over-the-counter" (OTC) orally administered antitussive. It is also used as an antitussive in combination with antihistamines in prescription (Rx) products for cold remedies.

Dextromethorphan may be used in the present invention in daily dosage amounts between about 1 mg and 1,000 mg and preferably between about 10 mg and about 500 mg depending on the age and weight of the animal to be treated and the type of pain to be treated. A typical daily dosage amount suitable for a human varies between about 1 mg and about 200 mg and preferably between about 10 mg and 100 mg. For example, a typical dosage amount of dextromethorphan hydrobromide effective in temporarily reducing pain associated with gastrointestinal dysfunction in an adult human male would be about 10 mg to about 50 mg administered in equal doses 1 to 4 times per day.

Antacids which may be used in combination with dextromethorphan in the present invention are conventional antacids which are well known and widely used in the treatment of a variety of excess acid related gastrointestinal dysfunctions including acid indigestion, heartburn, sour stomach and ulcers. Typical antacids include, for example, sodium bicarbonate, calcium carbonate, magnesium hydroxide and aluminum hydroxide. Antacids may be used in the present invention in combination with dextromethorphan in dosage amounts conventionally used for treatment of a variety of excess acid related gastrointestinal dysfunctions, as discussed above.

Anticholinergic drugs which may be used in combination with dextromethorphan in the present invention include those anticholinergics conventionally used in the treatment of peptic ulcers. Typical anticholinergic drugs used for this purpose include, for example, atropine, belladonna, homatropine, methscopolamine bromide and scopolamine hydrobromide. Anticholinergic drugs may be used in the present invention in combination with dextromethorphan in dosage amounts conventionally used in the treatment of peptic ulcers.

Histamine H_2 receptor antagonists which may be used in combination with dextromethorphan in the present invention include those histamine H_2 receptor antagonists which are conventionally used in the treatment of peptic ulcers, such as, for example, cimetidine and other histamine H_2 receptor antagonists including ranitidine and tiquinamide. Histamine H_2 receptor antagonists may be used in the present invention with

dextromethorphan in dosage amounts conventionally used in the treatment of peptic ulcers.

Antiflatulents which may be used in combination with dextromethorphan in the present invention include those antiflatulents which are conventionally used in the treatment of gastrointestinal dysfuntion, such as, for example, simethicone. Antiflatulents may be used in the present invention with dextromethorphan in dosage amounts conventionally used in the treatment of gastrointestinal dysfunction.

For therapeutic use, dextromethorphan will normally be administered as a pharmaceutical composition in the basic form or in the form of an addition salt with a pharmaceutically acceptable acid and in association with a pharmaceutical carrier therefor. Such addition salts include those with hydrochloric, hydrobromic, hydriodic, sulphuric and maleic acids and preferably hydrobromic.

Other pharmacologically active compounds may, in certain cases, be included in the composition. Advantageously, the composition will be made up in a dosage unit form appropriate to the desired mode of administration, for example, as a tablet, capsule, oral suspension, injectable solution or as a cream for topical administration.

The pharmaceutical compositions may be in a form suitable for oral use, for example, as tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide a pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets. These excipients may be, inert diluents, for example calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, maize starch, or alginic acid; binding agents, for example, starch, gelatine or acacia, and lubricating agents, for example, magnesium stearate or stearic acid. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

Formulations for oral use may also be presented as hard gelatine capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatine capsules wherein the active ingredient is mixed with an oil medium, for example, arachis oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active ingredients in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, for example, polyoxyethylene sorbitol monnoleate, or condensation product of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example, ethyl, or n-propyl, p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, or sodium or calcium cyclamate.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol.

The pharmaceutical compositions may be tableted or otherwise formulated so that for every 100 parts by weight of the composition there are present between 5 and 95 parts by weight of the active ingredient and preferably between 25 and 85 parts by weight of the active ingredient. The dosage unit form will generally contain between about 100 mg and about 500 mg of the active ingredient of the formula stated above.

From the foregoing formulation discussion, it is apparent that the composition of this invention can be administered topically, orally or parenterally. The term parenteral as used herein includes subcutaneous injection, intravenous, intramuscular, or intrasternal injection or infusion techniques.

The scientific basis of the discovery set forth herein is not fully understood; however, it is believed that dextromethorphan is able to exert its pain reducing activity by acting upon specific pain mediating receptors in the body, and particularly in the gastrointestinal area, associated with endogenous peptides recently discovered to be involved in the mediation of pain in animals including humans, which peptides are known as enkephalins.

The term "animals" as used herein refers generally to animals including humans. The phrase "pain associated with gastrointestinal dysfunction" as used herein refers to pain associated with a wide variety of gastrointestinal ailments and conditions including diseases or conditions, such as, for example, acid indigestion, heartburn, sour stomach, gas associated with the foregoing conditions and peptic ulcer disease of the esophagus, stomach and duodenum; a large and varied category of dyspepsia of unknown origin including cancer of the stomach,

infiltrative disease of the stomach including lymphoma; Crohn's disease, eosinophilic granuloma, tuberculosis, syphilis and sarcoidosis, abdominal lesions, chronic pancreatis, bilary disease, colic, Zollinger-Ellison syndrome, and other diseases and conditions of the gastrointestinal tract.

The following examples are shown for the purpose of illustration only and should not be deemed as limiting the scope of the invention.

EXAMPLE I

Patient, human male with diagnosis of duodenal ulcer, was awakened at 1:30 a.m. with gastric pain. Twenty mg dextromethorphan hydrobromide powder was dissolved in 100 cc of water and administered to the patient orally. Patient reported pain was relieved within 5 minutes and patient returned to sleep. Patient was again awakened with gastric pain at 4:05 a.m. Ten mg dextromethorphan hydrobromide powder was dissolved in 50 cc of water and administered orally. Patient reported pain was relieved within 10 minutes and patient returned to sleep. Patient again awakened at 6:00 a.m. with gastric pain. Twenty mg dextromethorphan hydrobromide powder was dissolved in 100 cc of water and administered to the patient orally. Patient reported pain was relieved in 5 minutes.

EXAMPLE II

Patient, human male with diagnosis of duodenal ulcer, was awakened with thoracic pain at 1:00 p.m. Patient orally administered two commercially available conventional antacid tablets, which did not relieve the pain. At 2:30 a.m., pain was reported as being more severe and two additional antacid tablets were taken with no pain relief. Discomfort continued until 4:00 a.m. when patient orally administered 20 mg of dextromethorphan hydrobromide in a conventional syrup. Pain was reported as being relieved within 15 minutes.

I claim:

1. A method of temporarily reducing pain associated with gastrointestinal dysfunction in humans comprising administering to a human having pain associated with gastrointestinal dysfunction an effective, pain reducing amount of dextromethorphan or a pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein the dextromethorphan is administered in a daily dosage regimen of about 1 mg to about 200 mg.

3. The method of claim 1 wherein the dextromethorphan is administered in a daily dosage regimen of about 10 mg to about 100 mg.

4. The method of claim 1 wherein the dextromethorphan is administered in the form of its hydrobromide salt.

5. The method of claim 4 wherein the dextromethorphan hydrobromide is administered orally.

6. The method of claim 1 wherein the dextromethorphan is administered in an oral dosage form selected from the group consisting of a tablet, capsule, lozenge, syrup, suspension and elixir.

7. The method of claim 6 wherein the oral dosage form additionally comprises an effective, gastric acid neutralizing amount of an antacid.

8. The method of claim 6 wherein the oral dosage form additionally comprises an effective gas inhibiting amount of an antiflatulent.

9. The method of claim 8 wherein the antiflatulent is simethicone.

10. The method of claim 6 wherein the oral dosage form additionally comprises an effective, gastric acid neutralizing amount of an antacid and an effective, gas inhibiting amount of an antiflatulent.

* * * * *

EXHIBIT D

PRESCRIPTION AND OTC DRUG PRODUCT PATENT AND EXCLUSIVITY LIST

See report footnote for information regarding report content

APPL/PROD NO	PATENT NO	PATENT EXPIRATON DATE	PATENT CODES	EXCLUSIVITY CODE(S)	EXCLUSIVITY EXPIRATION DATE
OMEPRAZOLE; PRILOSEC					
019810 001	4786505*PED	Oct 20, 2007		U-108	
	4853230*PED	Oct 20, 2007		U-108	
	6147103	Oct 09, 2018			
	6147103*PED	Apr 09, 2019			
	6150380	Nov 10, 2018			
	6150380*PED	May 10, 2019			
	6166213	Oct 09, 2018			
	6166213*PED	Apr 09, 2019			
	6191148	Oct 09, 2018			
	6191148*PED	Apr 09, 2019			
OMEPRAZOLE; PRILOSEC					
019810 002	4786505*PED	Oct 20, 2007		U-108	
	4853230*PED	Oct 20, 2007		U-108	
	6147103	Oct 09, 2018			
	6147103*PED	Apr 09, 2019			
	6150380	Nov 10, 2018			
	6150380*PED	May 10, 2019			
	6166213	Oct 09, 2018			
	6166213*PED	Apr 09, 2019			
	6191148	Oct 09, 2018			
	6191148*PED	Apr 09, 2019			
OMEPRAZOLE; PRILOSEC					
019810 003	4786505*PED	Oct 20, 2007		U-108	
	4853230*PED	Oct 20, 2007		U-108	
	6147103	Oct 09, 2018			
	6147103*PED	Apr 09, 2019			
	6150380	Nov 10, 2018			
	6150380*PED	May 10, 2019			
	6166213	Oct 09, 2018			
	6166213*PED	Apr 09, 2019			
	6191148	Oct 09, 2018			
	6191148*PED	Apr 09, 2019			
OMEPRAZOLE MAGNESIUM; PRILOSEC OTC					
021229 001	4786505*PED	Oct 20, 2007			
	4853230*PED	Oct 20, 2007			
	5690960	Nov 25, 2014			
	5753265	Jun 07, 2015			
	5817338	Oct 06, 2015			
	5900424	May 04, 2016			
	6403616	Nov 15, 2019			
	6428810	Nov 03, 2019			
OMEPRAZOLE; SODIUM BICARBONATE; ZEGERID					
021636 001	5840737	Jul 16, 2016		U-588	
	6489346	Jul 16, 2016	DS DP	U-588	
	6645988	Jul 16, 2016	DS DP		
	6699885	Jul 16, 2016		U-588	
	6780882	Jul 16, 2016	DS DP		
OMEPRAZOLE; SODIUM BICARBONATE; ZEGERID					
021636 002	5840737	Jul 16, 2016		U-624	
	5840737	Jul 16, 2016		U-623	
	6489346	Jul 16, 2016	DS DP	U-623	
	6489346	Jul 16, 2016	DS DP	U-624	
	6645988	Jul 16, 2016	DS DP		
	6699885	Jul 16, 2016		U-623	
	6699885	Jul 16, 2016		U-624	
	6780882	Jul 16, 2016	DS DP		
OMEPRAZOLE; SODIUM BICARBONATE; ZEGERID					
021849 001	6489346	Jul 16, 2016	DS DP	U-588	
	6645988	Jul 16, 2016	DS DP		
	6699885	Jul 16, 2016		U-588	
OMEPRAZOLE; SODIUM BICARBONATE; ZEGERID					
021849 002	6489346	Jul 16, 2016	DS DP	U-623	
	6645988	Jul 16, 2016	DS DP		
	6699885	Jul 16, 2016		U-623	

PATENT AND EXCLUSIVITY TERMS

PATENT USE

U-575 LOTEMAX OPTHALMIC SUSPENSION IS INDICATED FOR THE TREATMENT OF STEROID RESPONSIVE CONDITIONS OF THE PALPEBRAL BULBAR CONJUNCTIVA, CORNEA AND ANTERIOR SEGMENT OF THE GLOBE

U-576 ALREX OPTHALMIC SUSPENSION IS INDICATED FOR THE TEMPORARY RELIEF OF THE SIGNS AND SYMPTOMS OF SEASONAL ALLERGIC CONJUNCTIVITIS.

U-577 TREATMENT OF BENIGN PROSTATIC HYPERPLASIA WITH FINASTERIDE IN COMBINATION WITH DOXAZOSIN

U-578 TREATMENT OF COMMUNITY ACQUIRED PNEUMONIA, ACUTE EXACERBATION OF CHRONIC BRONCHITIS, AND ACUTE BACTERIAL SINUSITIS CAUSED BY SUSCEPTIBLE STRAINS OF DESIGNATED MICROORGANISMS IN PATIENTS 18 YEARS AND OLDER

U-579 TREATMENT OF EPILEPSY AND/OR MIGRAINE

U-580 TREATMENT OF DISORDERS OF THE SEROTONERGIC SYSTEM SUCH AS DEPRESSION AND ANXIETY-RELATED DISORDERS

U-581 METHOD OF TREATING A CONDITION CAPABLE OF TREATMENT BY INHALATION, E.G. ASTHMA, COMPRISING ADMINISTRATION OF A FORMULATION CLAIMED IN US PATENT NO. 6743413

U-582 METHOD FOR THE TREATMENT OF A RESPIRATORY DISORDER, E.G. ASTHMA, COMPRISING ADMINISTERING AN EFFECTIVE AMOUNT OF AN AEROSOL COMPOSITION TO A PATIENT FROM A METERED DOSE INHALER SYSTEM AS CLAIMED IN US PATENT NO 6253762

U-583 METHOD FOR THE TREATMENT OF A RESPIRATORY DISORDER, E.G. ASTHMA, COMPRISING ADMINISTERING TO A PATIENT BY INHALATION, A METERED AEROSOL DOSE OF A DRUG FORMULATION FROM THE METERED DOSE INHALER SYSTEM CLAIMED IN US 6546928

U-584 SINGLE-DOSE ADMINISTRATION BY THE EPIDURAL ROUTE, AT THE LUMBAR LEVEL, FOR THE TREATMENT OF PAIN FOLLOWING MAJOR SURGERY

U-585 TO PROMOTE WEIGHT GAIN AFTER WEIGHT LOSS IN CERTAIN TYPES OF PATIENTS

U-586 AN INTERMEDIATE RELEASE NICOTINIC ACID FORMULATION SUITABLE FOR ORAL ADMINISTRATION ONCE-A-DAY AS A SINGLE DOSE FOR TREATING HYPERLIPIDEMIA WITHOUT CAUSING DRUG-INDUCED HEPATOTOXICITY OR ELEVATIONS IN URIC ACID OR GLUCOSE OR BOTH

U-587 USE OF EPLERENONE IN COMBINATION WITH AN ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITOR (AND OPTIONALLY A DIURETIC) FOR TREATING CONGESTIVE HEART FAILURE AND HYPERTENSION

U-588 SHORT-TERM TREATMENT OF ACTIVE DUODENAL ULCER; TREATMENT OF HEARTBURN AND OTHER SYMPTOMS ASSOCIATED WITH GERD; SHORT-TERM TREATMENT OF EROSIVE ESOPHAGITIS; MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS

U-589 METHOD FOR TREATMENT OF A RESPIRATORY DISORDER, E.G., BRONCHOSPASM, COMPRISING ADMINISTERING AN EFFECTIVE AMOUNT OF AN AEROSOL COMPOSITION TO A PATIENT FROM A METERED DOSE INHALER SYSTEM AS CLAIMED IN U.S. PATENT NO 6131966

U-590 METHOD FOR TREATMENT OF A RESPIRATORY DISORDER,E.G ,BRONCHOSPASM,COMPRISING ADMINISTERING TO A PATIENT BY ORAL OR NASAL INHALATION A DRUG FORMULATION BY USING THE METERED DOSE INHALER SYSTEM AS CLAIMED IN US PATENT NO 6532955

U-591 TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER USING A DOSAGE FORM WHICH PROVIDES ONCE-DAILY ORAL ADMINISTRATION OF A PHENIDATE DRUG

U-592 TREATMENT OF PRIMARY HYPERCHOLESTEROLEMIA. MIXED HYPERLIPIDEMIA AND/OR HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HOFH)

U-593 TREATMENT OF PRIMARY HYPERCHOLESTEROLEMIA. MIXED HYPERLIPIDEMIA AND/OR HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HOFH)

U-594 PREVENTION OF POSTMENOPAUSAL OSTEOPOROSIS

U-595 35 MG ORALLY ONCE A WEEK FOR PREVENTION OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN; 35 MG ORALLY ONCE A WEEK FOR TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN

U-596 TREATMENT OF HORMONE RECEPTOR POSITIVE METASTATIC BREAST CANCER IN POSTMENOPAUSAL WOMEN WITH DISEASE PROGRESSION FOLLOWING ANTIESTROGEN THERAPY

U-597 FORTEO IS INDICATED FOR THE TREATMENT OF POST MENOPAUSAL WOMEN WITH OSTEOPOROSIS WHO ARE AT HIGH RISK FOR FRACTURE

U-598 PROPHYLACTIC TREATMENT OF MIGRAINE

U-599 METHOD FOR TREATING ALLERGIC CONJUNCTIVITIS

U-600 A METHOD OF TREATING A PATIENT IN NEED OF OPHTHALMIC ANTIMICROBIAL THERAPY WITH LEVOFLOXACIN

U-601 TREATMENT OF BIPOLAR DISORDERS

U-602 SIGNS AND SYMPTOMS OF OSTEOARTHRITIS, RHEUMATOID ARTHRITIS IN ADULTS, AND/OR PAUCIARTICULAR OR POLYARTICULAR COURSE JUVENILE RHEUMATOID ARTHRITIS, ACUTE PAIN IN ADULTS; PRIMARY DYSMENORRHEA; AND/OR ACUTE MIGRAINE ATTACKS IN ADULTS

U-603 METHOD OF TREATING INFECTIONS COMPRISING ORALLY ADMINISTERING AN EFFECTIVE AMOUNT OF THE FDA APPROVED ORAL SUSPENSION

U-604 METHOD OF LOWERING BLOOD GLUCOSE BY ONCE DAILY ADMINISTRATION

U-605 TREATMENT OF MAJOR DEPRESSIVE DISORDER(MDD);ALTHOUGH THE MEHCHANISM OF THE ANTIDEPRESSANT ACTION OF DULOXETINE IN HUMANS IS UNKNOWN, IT IS BELIEVED TO BE RELATED TO ITS POTENTIATION OF SERATONERGIC AND NORADRENERGIC ACTIVITY IN THE CNS

U-606 USE OF IRINOTECAN IN COMBINATION WITH 5-FLUOROURACIL AND LEUCOVORIN FOR THE TREATMENT OF METASTATIC COLRECIAL CANCER

U-607 CANCIDAS IS INDICATED FOR EMPIRICAL THERAPY FOR PRESUMED FUNGAL INFECTIONS IN FEBRILE, NEUTROPENIC PATIENTS

U-608 USE OF QUINOLONE COMPOUNDS AGAINST PNEUMOCOCCAL PATHOGENIC BACTERIA

PATENT AND EXCLUSIVITY TERMS

PATENT USE

U-609	USE OF QUINOLONE COMPOUNDS AGAINST QUINOLONE-RESISTANT PNEUMOCOCCAL PATHOGENIC BACTERIA
U-610	ATROVENT HFA (IPRATROPIUM BROMIDE HFA) INHALATION AEROSOL IS INDICATED AS A BRONCHODILATOR FOR MAINTENANCE TREATMENT OF BRONCHOSPASM ASSOCIATED WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE, INCLUDING CHRONIC BRONCHITIS AND EMPHYSEMA
U-611	METHOD OF USING DESLORATADINE TO TREAT SEASONAL AND PERENNIAL ALLERGIC RHINITIS, PRURITIS, AND CHRONIC IDIOPATHIC URTICARIA IN PATIENTS 2 YEARS OF AGE AND OLDER
U-612	TREATMENT OF SEASONAL ALLERGY SYMPTOMS WITH NASAL CONGESTION IN ADULTS AND CHILDREN 12 YEARS OF AGE AND OLDER
U-613	REDUCTION OF SERUM PHOSPHATE
U-614	TREATMENT OF SEXUAL DYSFUNCTION
U-615	ADJUNCTIVE THERAPY TO DIET IN ADULTS TO REDUCE LDL-C, TOTAL-C, TRIGLYCERIDES AND APO B, AND INCREASE HDL-C IN PATIENTS WITH PRIMARY HYPERCHOLESTEROLEMIA OR MIXED DYSLIPIDEMIA (TYPES IIA, IIB) AND TO TREAT HYPERTRIGLYCERIDEMIA (TYPES IV, V)
U-616	MANAGEMENT OF PERSISTENT, MODERATE TO SEVERE PAIN IN PATIENTS REQUIRING CONTINUOUS, AROUND-THE-CLOCK ANALGESIA WITH A HIGH POTENCY OPIOID FOR AN EXTENDED PERIOD OF TIME GENERALLY WEEKS TO MONTHS OR LONGER
U-617	TREATMENT OF ACUTE PROMYELOGENOUS LEUKEMIA (APL)
U-618	USE OF ROSUVASTATIN CALCIUM TO REDUCE ELEVATED TOTAL-C, LDL-C, APOB, NONHDL-C OR TG LEVELS; TO INCREASE HDL-C IN ADULT PATIENTS WITH PRIMARY HYPERLIPIDEMIA OR MIXED DYSLIPIDEMIA; AND TO SLOW THE PROGRESSION OF ATHEROSCLEROSIS
U-619	TREATMENT OF MALIGNANT NEOPLASM
U-620	TREATMENT OF INSOMNIA
U-621	METHOD OF TREATING CANCER
U-622	TREATMENT OF VEGF MEDIATED OCULAR DISEASE
U-623	SHORT TERM TREATMENT OF ACTIVE BENIGN GASTRIC ULCER
U-624	REDUCTION OF RISK OF UPPER GASTROINTESTINAL BLEEDING IN CRITICALLY ILL PATIENTS
U-625	ALLERGIC RHINITIS OR NASAL POLYPS
U-626	CLOLAR IS INDICATED FOR THE TREATMENT OF PEDIATRIC PATIENTS 1 TO 21 YEARS OLD WITH RELAPSED OR REFRACTORY ACUTE LYMPHOBLASTIC LEUKEMIA AFTER AT LEAST TWO PRIOR REGIMENS
U-627	TREATMENT OF PATIENTS USING EXTENDED-RELEASE CARBAMAZEPINE
U-628	USE OF AVANDIA IN COMBINATION WITH A SULFONYLUREA, AND IN COMBINATION WITH METFORMIN AND A SULFONYLUREA TO IMPROVE GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2 DIABETES MELLITUS
U-629	METHOD OF INDUCING A HYPNOTIC OR SEDATIVE EFFECT IN A HUMAN BY ADMINISTERING ESZOPICLONE
U-630	TREATING URINARY INCONTINENCE BY ADMINISTERING AN EXTENDED-RELEASE FORM OF DARIFENACIN
U-631	TREATING A DISEASE OF ALTERED MOTILITY OR TONE OF SMOOTH MUSCLE BY ADMINISTERING A MUSCARINIC RECEPTOR ANTAGONIZING AMOUNT OF DARIFENACIN
U-632	METHOD OF TREATMENT OF CANCER BY ADMINISTERING PARTICLES OF PACLITAXEL THAT HAVE A PROTEIN COATING
U-633	METHOD FOR TREATMENT OF TUMORS BY ADMINISTERING PACLITAXEL AT A DOSE IN THE RANGE OF ABOUT 30MG/METER SQUARE TO ABOUT 100MG/METER SQUARE IN A PHARMACEUTICALLY ACCEPTABLE FORMULATION THAT DOES NOT CONTAIN CREMOPHOR
U-634	METHOD FOR DELIVERY OF A BIOLOGIC (INCLUDING ANTINEOPLASTIC AGENTS) BY ADMINISTERING TO A PATIENT AN EFFECTIVE AMOUNT OF A BIOLOGIC AS A SOLID OR LIQUID WITH A POLYMERIC BIOCOMPATIBLE MATERIAL
U-635	TREATMENT OF GERD, MAINTENANCE OF HEALING OF EROSIVE ESOPHAGITIS AND RISK REDUCTION OF NSAID ASSOCIATED GASTRIC ULCERS
U-636	TREATMENT OR PREVENTION OF BRONCHOSPASM OR ASTHMATIC SYMPTOMS
U-637	TREATMENT OF DIABETES WITH AN AMYLIN AGONIST
U-638	TREATMENT OF DIABETES WITH AN AMYLIN AGONIST, INCLUDING WITH INSULIN
U-639	TREATMENT OF A MAMMAL HAVING A NEED OF OR REDUCED ABILITY TO PRODUCE INSULIN WITH AN INSULIN AND AN AMYLIN SUCH AS PRAMLINTIDE
U-640	USE OF AN AMYLIN AGONIST TO REDUCE GASTRIC MOTILITY AND TREAT POST PRANDIAL HYPERGYLCEMIA
U-641	USE OF AN AMYLIN AGONIST HAVING SPECIFIED BINDING ACTIVITY TO REDUCE GASTRIC MOTILITY, INCLUDING USE THROUGH PARENTERAL ADMINISTRATION
U-642	TREATMENT AND PREVENTION OF OSTEOPOROSIS
U-643	THE SHORT TERM TREATMENT (UP TO 10 DAYS) IN PTS HAVING GASTROESOPHAGEAL REFLUX DISEASE (GERD) AS AN ALTERNATIVE TO ORAL THERAPY IN PTS WHEN THERAPY WITH NEXIUM CAPSULES IS NOT POSSIBLE OR APPROPRIATE
U-644	TREATMENT OF SEASONAL ALLERGIC RHINITIS
U-645	TREATMENT OF ASTHMA
U-646	METHOD OF TREATING OTITIS
U-647	TREATMENT OF OSTEOPOROSIS IN POST MENOPAUSAL WOMEN AND/OR THE TREATMENT TO INCREASE BONE MASS IN MEN WITH OSTEOPOROSIS
U-648	THE TREATMENT OF OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN AND/OR THE TREATMENT TO INCREASE BONE MASS IN MEN
U-649	A METHOD FOR TREATING A TUMOR DISEASE

EXHIBIT E

Online Medical Dictionary

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Search GO

A | B | C | D | E | F | G | H | I | J | K | L | M | N | O | P | Q | R | S | T | U | V | W | X | Y | Z

solid

1. Firm; compact; not fluid; without interstices or cavities; not cancellous
2. A body that retains its form when not confined; one that is not fluid, neither liquid nor gaseous

[L. *solidus*]

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